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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,365	04/13/2004	Gavril Pasternak	62069DIV2(51590)	4859

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EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,365	PASTERNAK ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,16-20 and 22-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,16-20 and 22-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/25/2007 has been entered.

Response to Arguments

Applicant's arguments filed 1/25/2007 have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the applicants have argued that the synergism between morphine and butamben was unexpected especially due to the fact that lidocaine and butamben are different structurally (an amide versus an ester) and in their respective metabolic properties. The examiner respectfully points out that lidocaine and butamben both act via the same mechanism of action as clearly presented in the last office action. The applicant's are correct that the compounds have differing structures and potentially different metabolic properties, however as the mechanism of action is identical, the metabolic properties of the individual compounds are irrelevent to the determination of the obviousness of synergism. The examiner has clearly set forth the reasoning for the obviousness rejection and why synergism was to be expected. The metabolism of compounds having the same mechanism of action is useful here only in the determination of an optimal compound for use. In the present case the examiner has laid out why one would be motivated to choose butamben for use with morphine based primarily on the absorption and metabolic properties of butamben as set forth in the 103(a) rejection of record (poor aqueous solubility, less systemic absorption, lower toxicity).

The applicant's have submitted a declaration and a paper in support of their amendment/arguments presented. The examiner notes that the declaration and paper are in support of the assertion that there is a synergistic analgesia when morphine and butamben are topically co administered. The examiner agrees that such synergy is indeed present. The examiner does however assert that this synergy was expected due to the many references (presented by applicant as prior art and as detailed below in the art rejection) demonstrating synergy between morphine/lidocaine and morphine/bupivacaine. As lidocaine, bupivacaine and butamben all posses the same mechanism of action and as lidocaine and bupivacaine have demonstrable synergy with morphine it would be reasonable to one of ordinary skill in the art that other local anesthetics acting through the same mechanism of action would posses similar synergy with morphine. Thus though synergy has been demonstrated by the applicant's, it is not an unexpected result.

For the reasons set forth above and for the reasons of record the 103(a) rejections are maintained.

The 103(a) rejections are reproduced below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 16-20, 22-26 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoji et al. (Interaction of Intrathecally Infused Morphine and Lidocaine in Rats (Part I): Synergistic Antinociceptive Effects, Anesthesiology, December 1998, vol. 89(6), pp 1455-1463), in view of Goodman and Gilman (The Pharmacological Basis of Therapeutics, seventh edition, pp. 302-305 and pp 310-312), in view of Elkhoury et al. (US Patent No. 5589480) and further in view of Ptchelintsev et al. (US Patent No. 5834513).

Yoji et al. teach, on page 9, that morphine and lidocaine have a synergistic antinociceptive interaction in both bolus injections and in continuous coinfusion in which the agents are administered in small volumes and low concentrations. Further Yoji et al. notes that in a recent study it was shown that morphine and bupivacaine induced a faster onset and a modest hypoalgesic effect than when administered separately. On page 10, Yoji et al., teach that different opioid receptor subtypes have different characteristics and demonstrate different antinociceptive effects; further individual local anesthetics have different features, such as potency, duration, and motor block. Thus different opioid sub-types can have differing mechanisms of action, whereas the local anesthetics (like lidocaine and bupivacaine) have the same mechanism of action but differ in their pharmacological properties.

Yoji et al. does not teach the synergistic topical administration of morphine with butamben.

Goodman and Gilman teach, on pages 302-303 that local anesthetics have many actions in common and their primary mechanism of action involves a block of conduction by decreasing the large transient increase in the permeability of the membrane to sodium ions that is produced by a slight depolarization of the membrane. On page 310 the pharmacological action of lidocaine and procaine are as previously detailed (see above mechanism of action). On page 312 Goodman and Gilman detail two local anesthetics with low aqueous solubility, namely benzocaine (structurally identical to procaine without the terminal diethylamino group) and butamben picrate. It is taught that these compounds can be applied directly to wounds and ulcerated surfaces

as their poor solubility makes their systemic absorption too slow to be toxic. Further when applied they remain localized for long periods of time to produce a sustained anesthetic action.

Elkhoury et al. teaches the topical administration of an opioid drug, such as morphine, for producing analgesic effect in a localized peripheral area without transdermal migration of the opioid drug into the blood stream (Abstract; col. 2, lines 51-60; col. 4, lines 46-57). Administration to the skin is taught (Figures 1 and 2). Elkhoury et al. does not teach the claimed concentrations or the inclusion of butamben.

Ptchelintsev et al. teaches that butamben is a topical analgesic (col. 8, lines 1-2).

It would have been obvious to one of ordinary skill in the art that butamben could be used in Yuji et al's. antinociception opioid and local anesthetic composition as Yuji et al. teach the antinociception composition of morphine and lidocaine, and further teach that it is known that administration of morphine with lidocaine results in a synergistic antinociceptive effect. As Goodman and Gilman demonstrate local anesthetics have the same mechanism of action (sodium ion effect) and differ in their potency, duration and modes of administration with butamben being considered a low aqueous soluble compound suitable for topical administration with a long duration of action and low toxicity profile. One would be motivated to use butamben in lieu of lidocaine to take advantage of the lower toxicity and longer duration of action. One would have expected that butamben would posses synergistic activity with morphine as butamben's mechanism of action is the same as lidocaine and further as Yoji et al. point out that

synergistic activity has been seen with another local anesthetic (bupivacaine) in conjunction with morphine.

Elkhoury and Ptchelintsev demonstrate that morphine and butamben can be formulated as topical compositions.

The examiner respectfully points out: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

It is noted that Elkhoury et al. teaches the compositions disclosed therein for achieving peripheral analgesia generally and that Ptchelintsev et al. teaches butamben, generally, as a topical analgesic. Accordingly, it would have been obvious to one of ordinary skill in the art to arrive at the concentrations claimed because "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claims 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoji et al. (Interaction of Intrathecally Infused Morphine and Lidocaine in Rats (Part I): Synergistic Antinociceptive Effects, Anesthesiology, December 1998, vol. 89(6), pp 1455-1463), in view of Goodman and Gilman (The Pharmacological Basis of Therapeutics, seventh edition, pp. 302-305 and pp 310-312), in view of Elkhoury et al.

(US Patent No. 5589480) and further in view of Ptchelintsev et al. (US Patent No. 5834513) as applied to claims 11, 16-20, 22-26 and 33 above, and further in view of Mayer et al. (USPN 5840731).

Yoji et al., Goodman and Gilman, Elkhoury et al. (US Patent No. 5589480) and Ptchelintsev et al. (US Patent No. 5834513) apply as disclosed above. The reference lacks a teaching of an NMDA receptor antagonist.

Mayer et al. teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic is significantly enhanced by the addition of an NMDA receptor antagonist (Abstract). Mayer et al. teaches compositions comprising a first analgesic, a second component, and an analgesia-enhancing amount of an NMDA receptor antagonist and methods of treatment for alleviating pain by the administration thereof (col. 1, lines 6-27; col. 2, lines 30-col. 3, line 5; col. 4, line 67-col. 5, line 13). Analgesics are taught to be selected from fentanyl, morphine, etc. (col. 3, lines 57-65). NMDA receptor antagonists are taught to be selected from ketamine, etc. (col. 4, lines 33-50).

It would have been obvious to one of ordinary skill in the art to administer a topical composition comprising the morphine, butamben and an NMDA receptor antagonist because (1) Elkhoury et al. and Ptchelintsev et al. teach the morphine and butamben, respectively, as analgesics suitable for topical administration; and (2) Mayer et al. teaches that the addition of an NMDA receptor antagonist (e.g. ketamine) to an analgesic composition is known in the art to significantly enhance the analgesia provided thereby. One would have been motivated to prepare and utilize such a

composition because of an expectation of success in providing a topical composition suitable for peripheral relief with significantly enhanced analgesic effects, as taught by Mayer et al.

It is noted that Mayer et al. teaches the NMDA receptor antagonists disclosed therein for achieving improved analgesia generally. Accordingly, it would have been obvious to one of ordinary skill in the art to arrive at the concentrations claimed because "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claims 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoji et al. (Interaction of Intrathecally Infused Morphine and Lidocaine in Rats (Part I): Synergistic Antinociceptive Effects, Anesthesiology, December 1998, vol. 89(6), pp 1455-1463), in view of Goodman and Gilman (The Pharmacological Basis of Therapeutics, seventh edition, pp. 302-305 and pp 310-312), in view of Elkhoury et al. (US Patent No. 5589480) and further in view of Ptchelintsev et al. (US Patent No. 5834513) as applied to claims 11, 16-20, 22-26 and 33 above, and further in view of Soo (USPN 5028595).

Yoji et al., Goodman and Gilman, Elkhoury et al. (US Patent No. 5589480) and Ptchelintsev et al. (US Patent No. 5834513) apply as disclosed above. Furthermore, it is noted that Elkhoury et al. specifically teaches the treatment of painful conditions associated with inflammation (col. 2, lines 51-60).

Soo teaches that morphine is known in the art for the treatment of peripheral neuropathy (col. 62-66).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat the claimed conditions because (1) Elkhoury et al. teaches that morphine is known in the art to treat painful inflammatory disorders in general; and (2) Soo teaches that morphine is known in the art to treat peripheral neuropathy. One would have been motivated to treat the claimed conditions with the morphine compositions of the invention because of an expectation of success in treating the pain associated with the conditions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER